Anticholinergic drug use and its association with self-reported symptoms among older persons with and without diabetes

Inkeri, Niina-Mari

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[1]School of Pharmacy, University of Eastern Finland, Kuopio, Finland

[2]Institute of Public Health and Clinical Nutrition, General Practice, University of Eastern Finland, Kuopio, Finland

[3]Inner Savo Health Center, Suonenjoki, Finland

[4]Ilmarinen Mutual Pension Insurance Company, Vantaa, Finland

[5]Department of Neurosurgery, Helsinki University Hospital, Helsinki, Finland

[6]Unit of Primary Health Care, Helsinki University Central Hospital, Helsinki, Finland

[7]Primary Health Care Unit, Kuopio University Hospital, Kuopio, Finland

[8]Central Finland Central Hospital, Jyväskylä, Finland

ouu;vrom7;m1;
Miia Tiihonen, School of Pharmacy, University of Eastern Finland, Kuopio, Finland.
Email: miia.tiihonen@uef.fi

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: Anticholinergic drug use has been associated with a risk of central and peripheral adverse effects. There is a lack of information on anticholinergic drug use in persons with diabetes. The aim of this study is to investigate anticholinergic drug use and the association between anticholinergic drug use and self-reported symptoms in older community-dwelling persons with and without diabetes.

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: The basic population was comprised of Finnish community-dwelling primary care patients aged 65 and older. Persons with diabetes were identified according to the ICD-10 diagnostic codes from electronic patient records. Two controls adjusted by age and gender were selected for each person with diabetes. This cross-sectional study was based on electronic primary care patient records and a structured health questionnaire. The health questionnaire was returned by 430 (81.6%) persons with diabetes and 654 (73.5%) persons without diabetes. Data on prescribed drugs were obtained from the electronic patient records. Anticholinergic drug use was measured according to the Anticholinergic Risk Scale. The presence and strength of anticholinergic symptoms were asked in the health questionnaire.

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: The prevalence of anticholinergic drug use was 8.9% in the total study cohort. There were no significant differences in anticholinergic drug use between persons with and without diabetes. There was no consistent association between anticholinergic drug use and self-reported symptoms.

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: There is no difference in anticholinergic drug use in older community-dwelling persons with and without diabetes. Anticholinergic drug use should be considered individually and monitored carefully.

anticholinergic burden, anticholinergic drug use, diabetes mellitus, older people

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Several drugs prescribed for common indications have anticholinergic properties.[1] Anticholinergic properties may be desired in the management of certain conditions (eg, urinary incontinence and Parkinson's disease). Numerous common drugs in different therapeutic groups may have anticholinergic properties, and identifying these properties may be challenging. Diabetes has been associated

with conditions for which drugs with anticholinergic properties may be prescribed (eg, depression and neuropathic pain).[2,3]

Anticholinergic drugs expose older people to adverse drug effects.[4] Older people are known to be particularly at increased risk of anticholinergic adverse effects due to a decrease in central cholinergic receptors and an increase in blood-brain barrier permeability.[5,6] Anticholinergic adverse drug effects may occur peripherally (eg, dry mouth, dry eyes and constipation) or centrally (eg, drowsiness, dizziness and confusion).[4] Furthermore, anticholinergic drug use has been associated with both cognitive and functional decline.[7-9] Anticholinergic drug use in older people may lead to further adverse health outcomes, including hospital admissions and more visits to general practitioners.[10]

There is limited previous research on anticholinergic drug use in specific populations. Anticholinergic drug use has been evaluated, for example in persons with cognitive impairment,[7] schizophrenia[11] and Parkinson's disease.[12,13] There are a few previous studies investigating anticholinergic drug use in persons with diabetes.[14,15] These studies have focused on management of overactive bladder syndrome. Anticholinergic drug use has been associated with a higher prevalence of diabetes in a previous Finnish study.[16]

Diabetes has been associated with polypharmacy and comorbidities.[17,18] In particular, people with type 2 diabetes are at a greater risk of polypharmacy.[19] Polypharmacy in people with diabetes can be justifiable. Nevertheless, polypharmacy has been associated with anticholinergic drug use and a greater anticholinergic burden.[20-23] Furthermore, diabetes has been associated with possible blood-brain barrier dysfunction, which may increase the risk of central adverse effects.[24-26]

The aim of this study was to evaluate anticholinergic drug use and its association with self-reported symptoms among community-dwelling older people with and without diabetes.

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This cross-sectional study was conducted in the communities of Suonenjoki and Rautalampi in Eastern Finland. The total population of the district was 10 793, and the basic population (N = 3093) was comprised of community-dwelling primary care patients aged 65 and older. Persons with diabetes (N = 540) were identified from primary care electronic patient records according to diagnostic codes E10 and E11 of the International Classification of Diagnoses (ICD-10).[27] The cohort included 12 subjects with type 1 diabetes. Two controls adjusted by age and gender were selected for each person with diabetes. A structured health questionnaire was mailed once to 527 persons with diabetes and 890 controls in 2015 (August-September). This study is a part of the ISDM study, which has been described previously elsewhere by Karjalainen et al.[28]

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Data on prescribed drugs were obtained from the primary care electronic patient records (Pegasos®, CGI Suomi Ltd, Helsinki, Finland). Regular medications (daily or at regular intervals) were considered. Medications were categorized according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system codes.[29]

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The Anticholinergic Risk Scale (ARS) created by Rudolph et al is one of several tools available for identifying a cumulative anticholinergic burden that may lead to adverse effects.[4,30] In this study, the anticholinergic burden was quantified using the ARS, which has been previously applied in numerous studies.[30] The ARS is based on a literature review and expert opinion.[4] The review encompassed the 500 most frequently prescribed medications within the Veterans Affairs Boston Healthcare System, excluding topical, ophthalmic, otologic and inhaled medication preparations. Medications were classified into four categories from 0 to 3 according to their anticholinergic activity (0, limited or none; 1, moderate; 2, strong; 3, very strong). At present, 40 of the 49 anticholinergic medications listed in the ARS are available in Finland.[31]

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A structured health questionnaire was used to obtain data on background variables (sex, age, education years, living arrangements), self-rated health, health-related quality of life, exercise, depressive symptoms, consumption of alcohol, smoking, comorbidities and self-reported symptoms.

Self-rated health was assessed based on a numerical rating scale from 1 to 5 (excellent-poor). Health-related quality of life was assessed using the EuroQol EQ-5D questionnaire.[32] The frequency, efficiency and duration of exercise were assessed based on Kasari's FIT Index.[33] Depressive symptoms were evaluated using the Geriatric Depression Scale (GDS-15).[34] Alcohol consumption was measured based on the Alcohol Use Disorders Identification Test (AUDIT-C).[35] History and frequency of smoking were asked. Comorbidity was defined according to a list of common chronic diseases (mental disorder, Parkinson's disease, dementia, musculoskeletal disorder, cardiovascular disease, cancer, chronic obstructive pulmonary disease, asthma) and calculated using the Charlson Comorbidity Index (CCI).[36]

In one part of the questionnaire, the participants were asked to assess whether they had experienced various symptoms: dry eyes, dry mouth, constipation, gastrointestinal dysfunction or dizziness. These symptoms present typical anticholinergic adverse effects in older people.[4] The participants ranked the severity of each symptom using a numerical rating scale from 0 to 10.

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The study was approved by the Inner Savo Health Care Federation of Municipalities (61 A/2015). The study protocol of the ISDM (Inner Savo Diabetes Mellitus) study was approved by the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland (256/2015). The study was conducted in accordance with the Helsinki's Declaration. The health questionnaire included an information letter explaining the use of the data, and returning the questionnaire was voluntary. The autonomy of the research subjects was respected, and only anonymous data were analysed. No harm to the subjects was possible, and the confidentiality of the subjects and research data was protected.

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Descriptive statistics include means and SDs (standard deviations) for continuous variables and numbers and percentages for categorical variables. Statistical comparisons were made using analysis of variance (ANOVA) and logistic models with covariates when appropriate. Models included groups (diabetes and the ARS) and their interaction. The STATA 15.0, StataCorp LP (College Station, TX, USA) statistical package, was used for the analyses.

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The health questionnaire was returned by 430 persons with diabetes (81.6%) and 654 controls (73.5%). Females constituted 50.9% of the respondents with diabetes and 54.4% of the respondents without diabetes. The demographic characteristics of the study cohort according to anticholinergic drug use are presented in Table 1.

Persons with diabetes had a higher mean age, fewer years of education, a lower EQ-5D score, a lower Kasari's FIT Index, mobility aids more often, a higher CCI (excluding diabetes), dementia more often, cardiovascular disease more often and a higher mean number of drugs compared with persons without diabetes. Persons using at least one anticholinergic drug were more often female, had a higher mean age, were more often

TABLE 1 Descriptive characteristics of the study population

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Female, (%)	318 (53.1)	38 (69.1)	193 (49.6)	26 (63.4)	0.39	0.006	0.80
Age, mean (SD)	74 (6)	75 (7)	75 (7)	77 (8)	0.024	0.009	0.23
Education, y, mean (SD)	9.9 (3.2)	9.9 (3.3)	9.3 (3.0)	9.2 (3.0)	0.006	0.89	0.64
Living alone, n (%)	184 (30.7)	24 (43.6)	136 (35.0)	20 (48.8)	0.36	0.010	0.97
Good self-rated health (1, 2, 3), n (%)	343 (57.3)	21 (38.2)	165 (42.4)	13 (31.7)	0.052	0.007	0.49
EQ-5D, mean (SD)	0.8 (0.2)	0.7 (0.2)	0.7 (0.2)	0.6 (0.3)	0.004	<0.001	0.80
No mobility aids, n (%)	502 (83.8)	45 (81.8)	279 (71.7)	20 (48.8)	<0.001	0.024	0.090
Kasari's FIT Index, mean (SD)	40 (22)	37 (24)	30 (22)	24 (16)	<0.001	0.084	0.51
GDS-15, mean (SD)	2.5 (2.7)	3.6 (4.0)	3.3 (3.0)	4.3 (3.5)	0.058	0.012	0.93
Smoking, n (%)	63 (10.5)	4 (7.3)	22 (5.7)	1 (2.4)	0.12	0.27	0.69
AUDIT-C, mean (SD)	2.0 (2.1)	2.0 (2.1)	1.9 (2.2)	1.4 (1.9)	0.084	0.27	0.36
CCI, mean (SD)							
Total	0.4 (0.7)	0.5 (0.7)	1.7 (1.0)	1.9 (1.1)	<0.001	0.051	0.44
Excluding diabetes	0.4 (0.7)	0.5 (0.7)	0.6 (0.9)	0.7 (1.0)	0.011	0.14	0.65
Mental disorder, n (%)	8 (1.3)	4 (7.3)	14 (3.6)	4 (9.8)	0.12	0.001	0.42
Parkinson's disease, n (%)	2 (0.3)	3 (5.5)	5 (1.3)	2 (4.9)	0.32	<0.001	0.24
Dementia, n (%)	27 (4.5)	3 (5.5)	27 (6.9)	7 (17.1)	0.026	0.12	0.29
Musculoskeletal disorder, n (%)	257 (42.9)	34 (61.8)	206 (53.0)	29 (70.7)	0.081	<0.001	0.99
Cardiovascular disease, n (%)	337 (56.3)	36 (65.5)	302 (77.6)	34 (82.9)	<0.001	0.17	0.92
Cancer C00-97 (malign tumour), n (%)	52 (8.7)	1 (1.8)	26 (6.7)	2 (4.9)	0.32	0.25	0.54
COPD/asthma, n (%)	44 (7.3)	9 (16.4)	42 (10.8)	7 (17.1)	0.43	0.016	0.53
Number of drugs (excluding ATC codes P, D, J, V), mean (SD)	2.0 (2.6)	6.0 (3.3)	3.6 (3.1)	7.0 (4.4)	0.003	<0.001	0.42

ATC codes: P, antiparasitic products, insecticides and repellents; D, dermatologicals; J, anti-infectives for systemic use; V, various (eg, allergens, diagnostic agents)[27]; ARS, Anticholinergic Risk Scale[2]; AUDIT-C, alcohol use disorders identification test[33]; CCI, Charlson Comorbidity Index[34]; COPD, chronic obstructive pulmonary disease; EQ-5D; EuroQol EQ-5D questionnaire[30]; GDS-15, Geriatric Depression Scale.[32]

living alone, less frequently had good self-rated health, had a lower EQ-5D score, more often had mobility aids, had higher mean GDS-15 scores, more often had a mental disorder, Parkinson's disease, a musculoskeletal disorder, COPD or asthma and had a higher mean number of drugs. There was no interaction between the groups (diabetes and the ARS).

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The use of anticholinergic drugs is described in detail in Table 2. The prevalence of anticholinergic drug use was 8.9% in the total study cohort. Anticholinergic drug use was not associated with having diabetes. Forty-one (9.5%) persons with diabetes had at least one ARS score, whereas 55 (8.4%) of the controls scored at least one. The highest level of anticholinergic burden was five scores (four of the persons without diabetes).

The anticholinergic drugs used in the cohort are shown in Table 3. The most frequently used anticholinergic drug groups were psychoanaleptics (32.1% of total anticholinergic use), antihistamines for systemic use (20.8%) and psycholeptics (19.8%) among both persons with and without diabetes. Twenty-four anticholinergic drugs were identified. The most frequently used anticholinergic drugs in the total cohort were mirtazapine (12.3%), cetirizine (12.3%), amitriptyline with psycholeptics (10.4%), amitriptyline (8.5%) and loratadine (8.5%).

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There was no consistent association between anticholinergic drug use and self-reported symptoms. Anticholinergic drug use was associated with a higher risk of constipation and dizziness in both groups when adjusted by age, gender, years of education, GDS-15, smoking, alcohol consumption and CCI (excluding diabetes). In addition to this, anticholinergic drug use was associated with a higher risk of dry eyes in the group with diabetes and a higher risk of dry mouth, gastrointestinal dysfunction and fatigue in the control group (in the adjusted model). The results in the adjusted model are shown in Figure 1.

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One-tenth of this older community-dwelling Finnish population used anticholinergic drugs, and anticholinergic drug use was not associated with having diabetes. The results suggest that the use of anticholinergic drugs in the study population is relatively low. In previous Finnish studies, the prevalence of anticholinergic drug use has varied from 16% among community dwellers to 55% among persons living in long-term wards (when measured using the ARS).[20,37,38] There are no known previous studies investigating the prevalence of anticholinergic drug use in persons with diabetes, whereupon it is not possible to compare the results with previous findings in similar populations. Persons with diabetes may be even better monitored because the healthcare system provides diabetes nurse services, for example. However, one previous Finnish study found diabetes to be more common in anticholinergic drug users than in non-users among home-dwelling older people, which shows that the association is unclear.[16] The disparity of the results may arise from differences between the study populations and anticholinergic drug scales.

Psychoanaleptics and psycholeptics composed approximately half of the anticholinergic drug use in the study cohort. These findings are mostly in line with a previous Finnish study using the ARS, which found risperidone, mirtazapine, olanzapine and hydroxyzine as the most frequently used anticholinergic drugs among persons living in long-term wards.[37] Low-dose administration of mirtazapine in the management of chronic insomnia is mentioned in the Finnish Good Care Guidelines.[39] Mirtazapine might have been chosen as a safer alternative to benzodiazepines or z-drugs.

In this study, we investigated the association between anticholinergic drug use and self-reported symptoms that may indicate adverse drug effects. There was no consistent association between anticholinergic drug use and symptoms evaluated although the ARS, and the association with anticholinergic symptoms has been validated.[4] Similarly with our study, a previous Finnish study did not find a consistent association between anticholinergic drug use and adverse drug events.[20] Anticholinergic drug use was defined according to the ARS, but the adverse outcomes differed from those in our study (eg, functional capacity and cognition). Another Finnish study using the ARS did not find an association between anticholinergic drug use and dry mouth or constipation.[38] Studies using different anticholinergic drug scales have shown dry mouth and constipation to be more prevalent among anticholinergic drug users.[23,40] We were not able to confirm the cause of symptoms; the symptoms may be both drug-related and disease-related.

One of the strengths of this study was the high response rate of the health questionnaire and the high validity of the data collection.

TABLE 2 Anticholinergic drug use among persons with and without diabetes

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0	599 (91.6)	389 (90.5)	988 (91.1)
1	18 (2.8)	12 (2.8)	30 (2.8)
2	14 (2.1)	15 (3.5)	29 (2.7)
3	19 (2.9)	12 (2.8)	31 (2.9)
4	0 (0.0)	2 (0.5)	2 (0.2)
5	4 (0.6)	0 (0.0)	4 (0.4)

TABLE 3 Anticholinergic drugs used by persons with and without diabetes

m|b1otbm;ub17u‡$o7;Q	o7b-0;|;v7mPwQ	b-0;|;v7mPwQ	6|-t7mPwQ
Cetirizine (R06AE07)	5 (8.1)	8 (18.2)	13 (12.3)
Mirtazapine (N06AX11)	8 (12.9)	5 (11.4)	13 (12.3)
Amitriptyline and psycholeptics (N06CA01)	8 (12.9)	3 (6.8)	11 (10.4)
Amitriptyline (N06AA09)	5 (8.1)	4 (9.1)	9 (8.5)
Loratadine (R06AX13)	7 (11.3)	2 (4.6)	9 (8.5)
Tizanidine (M03BX02)	5 (8.1)	2 (4.6)	7 (6.6)
Quetiapine (N05AH04)	1 (1.6)	5 (11.4)	6 (5.7)
Hydroxyzine (N05BB01)	1 (1.6)	3 (6.8)	4 (3.8)
Levodopa and decarboxylase inhibitor (N04BA02)	3 (4.8)	1 (2.3)	4 (3.8)
Olanzapine (N05AH03)	2 (3.2)	2 (4.6)	4 (3.8)
Pramipexole (N04BC05)	4 (6.5)	0 (0.0)	4 (3.8)
Risperidone (N05AX08)	3 (4.8)	1 (2.3)	4 (3.8)
Loperamide (A07DA03)	2 (3.2)	1 (2.3)	3 (2.8)
Pseudoephedrine, combinations (R01BA52)	2 (3.2)	1 (2.3)	3 (2.8)
Metoclopramide (A03FA01)	0 (0.0)	2 (4.6)	2 (1.9)
Oxybutynin (G04BD04)	1 (1.6)	1 (2.3)	2 (1.9)
Baclofen (M03BX01)	0 (0.0)	1 (2.3)	1 (0.9)
Clozapine (N05AH02)	0 (0.0)	1 (2.3)	1 (0.9)
Levodopa, decarboxylase inhibitor and COMT inhibitor (N04BA03)	0 (0.0)	1 (2.3)	1 (0.9)
Perphenazine (N05AB03)	1 (1.6)	0 (0.0)	1 (0.9)
Prochlorperazine (N05AB04)	1 (1.6)	0 (0.0)	1 (0.9)
Ranitidine (A02BA02)	1 (1.6)	0 (0.0)	1 (0.9)
Selegiline (N04BD01)	1 (1.6)	0 (0.0)	1 (0.9)
Trazodone (N06AX05)	1 (1.6)	0 (0.0)	1 (0.9)
Total	62 (100.0)	44 (100.0)	106 (100.0)

ATC, anatomical therapeutic chemical.

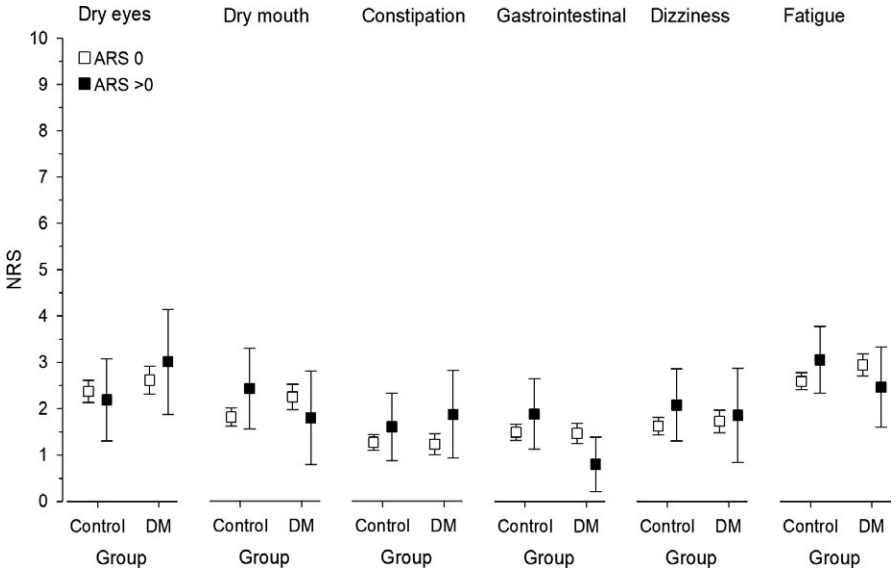

FIGURE 1 Self-reported symptoms among persons with and without diabetes (adjusted model). ARS, Anticholinergic Risk Scale; NRS, numerical rating scale

The health questionnaire provided thorough information on background variables, which enables comparison of the groups and adjustment for several potential confounders. The ARS has been validated in a veteran's population, and higher ARS scores have been associated with anticholinergic adverse effects.[4] Apart from that, the ARS has been previously applied to other studies evaluating the

association between anticholinergic medications and adverse drug effects.[20,38] Additionally, not only the presence but also the strength of symptoms was determined in this study.

This study has a few limitations. The study cohort was geographically restricted and represents the population of one primary care district in a semirural area in Eastern Finland. The findings cannot be directly generalized to other populations. Persons with diabetes represent persons able to live at home, which makes survival bias possible. Because of the cross-sectional design of the study, it was not possible to prove any causal relationship between anticholinergic drug use and self-reported symptoms. Although we obtained extensive information on background variables, only diagnosis of diabetes was confirmed from electronic patient records; other comorbidities were self-reported. We were not able to determine the onset or progression of diabetes exactly, but we can presume that the participants represent patients with a substantially long history of diabetes, since the study recruitment was performed according to an established diagnosis of diabetes 3 months before the questionnaire was sent. Lastly, self-reporting may underestimate adverse effects compared with adverse effects noted in the clinical examination.[41]

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There is no difference in anticholinergic drug use in older community-dwelling persons with and without diabetes. There is no consistent association between anticholinergic drug use and self-reported anticholinergic symptoms. Further studies are needed to confirm the impact of anticholinergic drugs on experienced symptoms in different subpopulations.

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The health questionnaire included an information letter explaining the use of the data, and returning the questionnaire was voluntary. The autonomy of the research subjects was respected, and only anonymous data were analysed. No harm to the subjects was possible, and the confidentiality of the subjects and research data was protected.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the Research Ethics Committee of the Northern Savo Hospital District, Kuopio, Finland (256/2015), and with the 1964 Helsinki's declaration and its later amendments or comparable ethical standards.

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No conflicts of interest have been declared.

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Miia Tiihonen http://orcid.org/0000-0002-5069-5045

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